

*REMARKS/ARGUMENTS**The Pending Claims*

Claims 5, 8, 10-12, 18, 20, and 32-35 are pending and are directed to a method of enhancing an immune response in a subject (claims 5, 8, 10-12, 32, and 34) and a method of treating a subject with a condition comprising a deficiency of at least one of memory B cells and plasma cells (claims 18, 20, 33, and 35).

Amendments to the Claims

Claims 5 and 18 have been amended to further clarify the claimed subject matter. In particular, claims 5 and 18 also have been amended to recite that the composition (comprising the (i) IL-21 polypeptide or (ii) variant thereof) induces differentiation of at least one B cell into one or more of a memory B cell and a plasma cell.

No new matter has been added by way of these amendments to the claims.

Summary of the Office Action

The Office rejects claims 5, 8, 10-12, 18, 20, and 32-35 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.

The Office claims 5, 8, 10-12, 18, 20, and 32-35 under 35 U.S.C. § 103(a) as allegedly obvious over Newell et al. (U.S. Patent Application Publication 2003/0138433) and Novak et al. (U.S. Patent Application Publication 2003/0125524).

Reconsideration of these rejections is hereby requested.

Discussion of the Indefiniteness Rejection

The Office contends that it is unclear which composition induces differentiation in claims 5 and 18, because claims 5 and 18 refer to two different compositions. Claims 5 and 18 (and, thus, claims 8, 10-12, 20, and 32-35 dependent thereon) have been amended to further clarify the claimed subject matter, thereby rendering moot the rejection.

Discussion of the Obviousness Rejection

The Office contends that it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention based on the teachings of the Newell and Novak references. The obviousness rejection is traversed for the following reasons.

For subject matter defined by a claim to be considered obvious, the Office must demonstrate that the differences between the claimed subject matter and the prior art “are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” 35 U.S.C. § 103(a); see also *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). The ultimate determination of whether an invention is or is not obvious is based on certain factual inquiries including: (1) the scope and content of the prior art, (2) the level of ordinary skill in the prior art, (3) the differences between the claimed invention and the prior art, and (4) objective evidence of nonobviousness. *Graham*, 383 U.S. at 17-18, 148 U.S.P.Q. at 467.

Consideration of the aforementioned *Graham* factors here indicates that the present invention, as defined by the pending claims, is unobvious in view of the cited references.

As regards the scope and content of the prior art, the Office contends that the Newell reference discloses a method for promoting an antigen-specific immune response comprising obtaining B cells that were isolated from a subject and contacting the B cells *in vitro* with a target antigen-conjugate to produce target antigen. The Office acknowledges that the Newell reference does not teach contacting a population of mature B cells or a B cell progenitor with IL-21; however, the Office contends that the Novak reference discloses α 11 ligand (i.e., IL-21) and discloses that α 11 ligand stimulates immune responses against B cell tumors, viruses, parasites, or bacteria. Additionally, the Office contends that the Novak reference discloses that α 11 ligand has an effect on the growth/expansion and/or differentiated state of B cells *in vivo*.

The Office contends that both the Newell and Novak references disclose methods for stimulating proliferative responses of mature B cells with various cytokines; therefore, the Office contends that it would have been obvious for one of ordinary skill in the art to attempt

to potentiate the immune response to an antigen and to enhance the therapeutic benefit to the host by replacing any of the IL-4, IL-5, IL-6, IL-9, IL-10, and/or IL-13 taught by the Newell reference with a α 11 ligand (IL-21) disclosed by the Novak reference to achieve the result of inducing an immune response in a subject, especially because the Novak reference discloses that the α 11 ligand (IL-21) is involved in the activation and proliferation of mature B cells in response to activating stimuli.

For purposes of the analysis here, and for the sake of argument, the level of ordinary skill can be considered to be relatively high, such that a person of ordinary skill in the art would have an advanced degree and/or several years of experience in the relevant field.

The present invention, as defined by the pending claims, is directed to a method of enhancing an immune response in a subject (claims 5, 8, 10-12, 32, and 34) and a method of treating a subject with a condition comprising a specific deficiency of at least one of memory B cells and plasma cells (claims 18, 20, 33, and 35), comprising (a) isolating a population of cells comprising one or more of a mature B cell and a B cell progenitor from the subject; (b) contacting the population of cells comprising at least one of a mature B cell and a B cell progenitor *ex vivo* with a composition comprising (i) an IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 or (ii) a variant of the amino acid SEQ ID NO: 1, wherein the variant comprises the amino acid sequence of SEQ ID NO: 1 except for 1-5 amino acid substitutions, deletions, or additions, and wherein the variant retains the ability to bind to the IL-21 receptor and produce a physiological effect produced by binding of the IL-21 polypeptide to the IL-21 receptor, wherein the population of cells optionally is contacted with at least one antigen, and wherein the composition induces differentiation of at least one B cell into one or more of a memory B cell and a plasma cell; (c) isolating the memory B cell, the plasma cell, or both; and (d) introducing at least one of the memory B cell and the plasma cell into the subject.

The invention is predicated on the inventors' discovery that contacting a population of cells comprising one or more of a mature B cell and a B cell progenitor with a composition comprising IL-21 induces differentiation of the mature B cell and/or B cell progenitor into one or more of a memory B cell and a plasma cell. In particular, the inventors discovered that IL-21 induces differentiation of human B cells into plasma cells and memory B cells

(see, for instance, Example 4 of the application). Prior to the inventors' discovery, one of ordinary skill in the art would not have recognized that contacting an isolated population of mature B cells and/or B cell progenitors with IL-21 would induce differentiation of human B cells into plasma cells and memory B cells (see paragraph 5 of the "Declaration Under 37 C.F.R. § 1.132 of Warren Leonard, M.D.," which is submitted herewith).

The Novak reference discloses that zalpha11 ligand (IL-21) stimulates the proliferation of B cells (i.e., increasing the population of undifferentiated B cells) in response to activating stimuli (see Example 44); however, the Novak reference does not provide any evidence that contacting IL-21 with a population of mature B cells and/or B cell progenitors results in the differentiation of the mature B cells and/or B cell progenitors into memory B cells and/or plasma cells, as required by the pending claims (see paragraphs 6 and 8 of the "Declaration Under 37 C.F.R. § 1.132 of Warren Leonard, M.D."). The Novak reference merely mentions that "[p]roteins of the present invention are useful for stimulating proliferation, activation, differentiation and/or induction or inhibition of specialized cell function of cells of the involved homeostasis of the hematopoiesis and immune function," wherein hematopoietic lineages include, but are not limited to, T cells, B cells, NK cells, dendritic cells, monocytes, macrophages, and epithelial cells (see paragraph 7 of the "Declaration Under 37 C.F.R. § 1.132 of Warren Leonard, M.D."). Thus, one of ordinary skill in the art, upon reading the Novak reference, would not have recognized that that contacting isolated mature B cells and/or B cell progenitors with IL-21 would induce differentiation of the B cells into plasma cells and memory B cells.

The Newell reference does not remedy the deficiencies of the Novak reference. As acknowledged by the Office, the Newell reference does not mention IL-21, let alone the ability of IL-21 to induce differentiation of mature B cells and/or B cell progenitors into one memory B cells and/or plasma cells (see paragraph 9 of the "Declaration Under 37 C.F.R. § 1.132 of Warren Leonard, M.D."). The Newell reference merely discloses that a primary encounter with an antigen can stimulate specific B cells to differentiate into cells that produce antibody at a high rate (plasma cells) and populations of memory cells (see paragraph 9 of the "Declaration Under 37 C.F.R. § 1.132 of Warren Leonard, M.D."). Thus, based on the disclosure of the Newell reference, one of ordinary skill in the art would not have recognized that contacting isolated mature B cells and/or B cell progenitors with a composition

comprising IL-21 would induce differentiation of the B cells into plasma cells and memory B cells.

Furthermore, neither of the cited references discloses isolating or purifying one or more of the memory B cell and the plasma cell (whose differentiation was induced by contacting mature B cells and/or B cell progenitors with IL-21) and introducing at least one of the memory B cell and the plasma cell into the subject, as required by the pending claims.

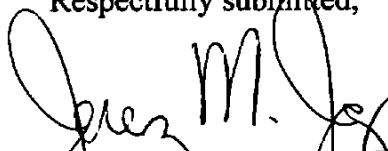
For the above-described reasons, the Novak and Newell references, when considered alone or in combination, do not teach or suggest all of the elements of the pending claims. It is only by considering the disclosure of the present application in improper hindsight that one of ordinary skill in the art at the relevant time would have been led to the presently claimed subject matter.

Considering all of the *Graham* factors together, it is clear that the present invention – as defined by the pending claims – would not have been obvious to one of ordinary skill in the art at the relevant time in view of the combined disclosures of the Newell and Novak references. Accordingly, the obviousness rejection should be withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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